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PERMSELECTIVE MEMBRANETechnical field of the invention

The present invention relates to a permselective asymmetric hollow fibre membrane for the separation of
5 toxic mediators from blood, comprised of at least one hydrophobic polymer and at least one hydrophilic polymer. Further, the present invention relates to a process for the preparation of such a membrane, and the use of said membrane in hemofiltration for treatment of toxic media-
10 tor related diseases.

Background of the invention

A significant number of patients in intensive care units die from a secondary complication known commonly as
15 "sepsis" or "septic shock". Medical illness, trauma, complication of surgery, and any human disease state, if sufficiently injurious to the patient, may develop into systemic inflammatory response syndrome ("SIRS"), multi-organ system dysfunction syndrome ("MODS"), and multi-
20 organ system failure ("MOSF").

The mechanism of SIRS is the excessive release of host derived inflammatory mediators, herein referred to as toxic mediators ("TM"). TM include various cytokines (tumor necrosis factor, TNF; the interleukins; inter-
25 feron), various prostaglandins (PG I.sub.2, E.sub.2, Leukotrienes), various clotting factors (platelet activating factor, PAF), various peptidases, reactive oxygen metabolites, and various poorly understood peptides which cause organ dysfunction (myocardial depressant factor,
30 MDF). If the inflammatory response is excessive, then injury or destruction to vital organ tissue may result in multiorgan dysfunction syndrome ("MODS"). Sepsis is the single most common cause of SIRS leading to MOSF.

Hemofiltration ("HF") was developed as a technique to control overhydration and acute renal failure in unstable patients and may use a hemofilter consisting of a cellulose derivatives or synthetic membrane (e.g., polysulfone, polyamide, etc.) fabricated as either a parallel plate or hollow fibre filtering surface. Current HF membranes, when used to treat acute renal failure associated with MOSF have been associated with incidental improvements in organ function other than the kidneys. However, these membranes remain deficient in the treatment of MOSF because their specific design characteristics prevent them from removing TM in the upper molecular weight range of recognized TM.

The pores of most conventional hemofiltration membranes allow passage of molecules up to 30,000 Daltons in water with very few membranes allowing passage of molecules up to 50,000 Daltons. The membranes used to treat renal failure were generally designed to achieve the following specific goals: (i) to permit high conductance of the aqueous phase of blood plasma water needed to permit the formation of ultrafiltrate at a fairly low transmembrane pressure (typically 20-40 mm Hg), which requires a relatively large pore size that incidentally passes molecules of up to 30,000 to 50,000 Daltons; and (ii) to avoid passage of albumin (e.g., 68,000 Daltons). Loss of albumin, and subsequently, oncotic pressure, could cause or aggravate tissue oedema and organ dysfunction (e.g., pulmonary oedema), so hemofilters are often designed to avoid this by having molecular weight exclusion limits well below the molecular weight of albumin (e.g., 68,000 Daltons).

During filtration of protein containing solutions, after only 20 min the accumulation of protein as a gel or polarization layer occurs on the membrane surface. This gel layer dramatically reduces effective pore size, reducing the filterable molecular weights by roughly 10-

40%. Therefore, pore sizes selected are somewhat larger than needed, anticipating a reduction in effective size.

US-A-5 571 418 discloses a novel method of continuous arteriovenous hemofiltration using a polysulfone or similar material, hollow fibre hemofilter with a molecular weight exclusion limit of up to 100,000 to 150,000 Daltons as therapeutic regimen for sepsis, multiple organ failure (MOF), systemic inflammatory response syndrome (SIRS) or other mediator-related diseases.

The device and process described in US-A-5,571,418 generally contemplates the use of large pore hemofiltration membranes with pore sizes to provide molecular weight exclusion limits of 100,000 to 150,000 Daltons in water. With these higher molecular weight cut-offs, these membranes are designed to remove a wider range of different IM's.

EP-A-0 305 787 discloses permselective asymmetric membranes suitable for hemodialysis and a process for the manufacturing thereof. Said membrane has a special three-layer structure having high diffusive permeability, comprising a first inner layer in the form of a dense rather thin skin, having a thickness below 1 μm and a maximum pore size of about 8 nm, responsible for the sieving properties, a second layer in the form of a sponge structure, having a thickness of about 1 to 15 μm and serving as a support for said first layer and a third layer in the form of a finger structure, giving the membrane a mechanical stability and having a thickness of about 20 to 60 μm . The membrane is manufactured by presolving the hydrophobic first polymer in a solvent, presolving the hydrophilic second polymer in a solvent of preferably the same kind, mixing the two solutions, extruding the mixture through the outer ring slit of a nozzle with two concentric openings, a precipitating liquid including a part of the hydrophilic second polymer flowing through the inner openings, to obtain a coagu-

lated membrane, which is subsequently washed and preferably dried.

Summary of the invention

5 The object of the present invention is to provide an improved permselective asymmetric hollow fibre membrane for the separation of toxic mediators from blood, comprised of at least one hydrophobic polymer and at least one hydrophilic polymer.

10 This object is achieved by a membrane, which allows passage of molecules having a molecular weight of 45 000 Daltons in presence of whole blood and having a molecular weight exclusion limit in water of about 200,000 Daltons.

15 A further object of the invention is to provide a process for the preparation of the membrane of the present invention.

This object is achieved by a process comprising the steps of

20 a) dissolving the at least one hydrophobic polymer and the at least one hydrophilic polymer in a solvent to form a polymer solution,

- b) extruding the formed polymer solution through an outer ring slit of a nozzle with two concentric openings,
- c) extruding a grafting solution

25 c) extruding a centre fluid through the inner opening of the nozzle, and

d) subsequently washing and preferably drying the membrane, wherein the polymer solution comprises 10-20 weight% hydrophobic polymer and 2-11 weight% hydrophilic polymer.

30 Yet another object of the invention is to provide a use of the membrane for treatment of toxic mediator related diseases, especially sepsis.

The present invention comprises a HF method using a novel membrane fabricated with a pore size capable of allowing passage of molecules of about 45,000 Daltons in presence of whole blood and having an exclusion limit in water of about 200,000 Daltons. The membrane of the

5

present invention is useful in treating human patients with SIRS-MOSF and provides for removal by filtration of the entire known range of TM.

By the membrane of the invention a high selectivity is achieved, i. e. a high removal of toxic mediators having a molecular weight of up to 45,000 Dalton is achieved at the same time as a low amount of albumin, having a molecular weight of 68,000 Dalton is lost. Moreover, the risk for proteins which penetrate into the membrane structure to be absorbed in the pore structure of the membrane and thus change the permeability of the membrane, is highly reduced.

Other objects, features, advantages and preferred embodiments of the present invention will become apparent from the following detailed description when taken in conjunction with the drawings and the appended claims.

Brief description of the drawings

Preferred embodiments of the present invention will now be described in more detail, reference being made to the enclosed drawings, in which:

Fig. 1a and 1b show scanning electron microscopic pictures of cross sections of the membrane structure according to a preferred embodiment of the invention,

Fig 2 shows a scanning electron microscopic picture of the inner surface of the membrane,

Fig 3a and 3b shows the sieving coefficients for two different membranes, a prior art standard "high flux membrane" and the membrane according to the invention,

Fig 4 shows the protein loss into the filtrate for a standard high flux membrane and for the membrane of the invention,

Fig 5 shows IL-6 values in plasma and filtrate 30 min after initiation of filtration by the membrane of the invention, and

Fig 6 shows the removal of circulating mediators in Renal Intensive Care (RIC)/sepsis for a standard high flux membrane and the membrane of the invention.

5 Detailed description of preferred embodiments

The present invention provides a permselective asymmetric hollow fibre membrane for use in a method of treating a pathophysiological state by filtering blood, comprising the steps of: withdrawing blood from a mammal;
10 filtering the blood; removing an ultrafiltrate of plasma; and returning said blood to the mammal. The methods of the present invention may use either continuous arterio-venous or continuous venovenous hemofiltration.

As used herein, the term "hemofiltration", HF,
15 refers to a process of filtering blood by a membrane with separation of all formed elements, all proteins larger than effective pore size, and retained plasma water and solute (these return to the patient) from ultrafiltrate.

As used herein, the term "ultrafiltrate" refers to
20 the filtered plasma water and solute and molecules (including target peptides and proteins) smaller than effective pore size.

The term "hollow fibre membrane" used throughout the application text is intended to cover everything from one
25 single hollow fibre up to several single hollow fibres and one or more bundles of such hollow fibres, each fibre having a filtrate side and a blood side.

The term "flat sheet membrane" used throughout the application text means a micropore containing flat
30 membrane having a filtrate side and a blood side.

As used herein, the term "Toxic Mediators", TM,
refers to a heterogeneous group of chemicals synthesized and released by human tissue. TM include the inflammatory mediators of SIRS (cytokines, prostaglandins, oxygen
35 metabolites), various clotting factors, various peptidases and various toxic peptides. The molecular weight range of known TM is 1,000-60,000.

As used herein, the term "hemofilter", refers to the filter used in hemofiltration. It is configured as either a series of parallel plates or as a bundle of hollow fibres. The blood path is from a blood inlet port, through the fibres or between the plates, then to a blood outlet port. Filtration of blood occurs at the membrane with ultrafiltrate forming on the side of the membrane opposite the blood. This ultrafiltrate accumulates inside the body of the filter contained and embodied by the filter jacket. This jacket has an ultrafiltrate drainage port.

As used herein, the term "extracorporeal circuit" refers to the system of plastic tubes attached to the hemofilter which is used clinically. The arterial line is the plastic tube which carries blood from artery or vein to the blood inlet port of the hemofilter. The venous line carries blood from the blood outlet port returning to a vein. The ultrafiltrate line carries ultrafiltrate from the ultrafiltrate drainage port on the filter jacket to a reservoir from which ultrafiltrate is discarded.

As used herein, the term "effective sieving coefficient (S)" refers to the physical property of a membrane to exclude or pass molecules of a specific molecular weight:

$$S = (\text{concentration in filtrate}) / (\text{concentration in feed})$$

For the purposes of the present invention, the appropriate membrane allows for passage of molecules in the range of toxic mediators of up to 45,000 Daltons in the presence of whole blood/blood proteins, which means the molecular weight of a substance having a sieving coefficient (S) of 0.9 in presence of whole blood.

As used herein the term "cut off" refers to "nominal cut off" which means the molecular weight of a substance having a sieving coefficient (S) of 0.1 in water.

The membrane, in a preferred embodiment of the present invention has a unique structure, including a specific 3-layer structure with an innermost layer, i. e. a blood contacting layer, having a glomerular structure of the skin with pores having a size in the nanoscale range. In Fig 1a and 1b cross sections of the membrane structure according to the invention are shown, and in Fig 2 a scanning electron microscopic picture of the inner surface of the membrane. Pore channels between glomerular polymer clusters consisting of a mixture of hydrophilic polymers and hydrophobic polymers are shown.

At least one hydrophilic polymer and at least one hydrophobic polymer are present in the membrane as domains on the surface. Preferably the hydrophobic polymer is present in an amount of 10-20 weight%, based on the weight of the membrane. The hydrophilic polymer is preferably present in an amount of 2-11 weight%, based on the weight of the membrane.

The hydrophobic polymer according to the invention may be chosen from the group consisting of polyarylether-sulfone (PAES), polypropylene (PP), polysulfone (PSU), polymethylmethacrylate (PMMA), polycarbonate (PC), polyacrylonitrile (PAN), polyamide (PA), or polytetrafluoroethylene (PTFE).

The hydrophilic polymer of the invention may be chosen from the group consisting of polyvinylpyrrolidone (PVP), polyethyleneglycol (PEG), polyvinylalcohol (PVA), and copolymer of polypropyleneoxide and polyethyleneoxide (PPO-PEO).

The membrane of the invention has in a preferred embodiment at least a 3-layer asymmetric structure. In the innermost layer of the hollow fibre a separation layer is present, having a thickness of $< 0.5 \mu\text{m}$ and containing pore channels, having a pore size of 15-60 nm, preferably 20-40 nm. The next layer in the hollow fibre membrane is the second layer, having the form of a sponge structure and in a preferred embodiment a thickness of

about 1-15 μm and serving as a support for said first layer. Then, there is the third layer, having the form of a finger structure. It provides like a framework a mechanical stability on the one hand; on the other hand it has through the high void volume a very low resistance of transport of molecules through the membrane. During the process the voids are filled with water and the water gives a lower resistance against diffusion and convection than a matrix with a sponge-filled structure having a lower void volume. Accordingly, the third layer gives the membrane a mechanical stability and has, in a preferred embodiment of the present invention, a thickness of 20 to 60 μm .

In Fig 3 the sieving coefficients for two different membranes, a prior art standard "high flux membrane" and the high cut off membrane according to the invention are shown. In Fig 4 the protein loss is illustrated. As may be seen from the figures the sieving coefficient of the membrane according to the present invention is superior to the high flux membrane and at the same time the loss of albumin is significantly lower in the membrane of the invention. According to a preferred embodiment of the invention the sieving coefficient for albumin in presence of whole blood is below 0,05.

Fig 5 and Fig 6 shows the removal of circulating mediators in Renal Intensive Care (RIC)/sepsis. According to the invention the sieving coefficient for IL-6 in presence of whole blood is 0.9-1.0.

In a preferred embodiment the membrane having the above described three-layer structure also includes a fourth layer, which is the outer surface of the hollow fibre membrane. In this preferred embodiment the outer surface has openings of pores in the range of 0.5-3 μm and the number of said pores are in the range of 10,000 to 150,000 pores/ mm^2 , preferably 20,000 to 100,000 pores/ mm^2 . This fourth layer preferably has a thickness of 1 to 10 μm .

An advantage of this embodiment is the provision of a hollow fibre membrane, which is non-sticky and is easy to handle. This results in less cracks and holes in the fibres during the manufacturing process, which in turn leads to less scrap in the manufacturing process. Another advantage is that the hollow fibre has less tendency to adhere to the hollow fibres adjacent in the bundle due to the high number of pores on the surface. Thus, the dialysate surrounding the hollow fibres during use has enhanced access to the hollow fibres since they are less inclined to adhere to each other.

This specific surface on the outside of the hollow fibre is achieved by modifying the spinning polymer solution composition only in the outer section of the hollow fibre membrane wall by penetration of water from a very specific steam/air atmosphere into the first 1-15 μm of polymer solution layer just before the precipitation from the inside arrives at this layer.

The manufacturing of the membrane according to the present invention follows a phase inversion process, wherein a polymer or a mixture of polymers is dissolved in a solvent to form a polymer solution. The solution is degassed and filtered and is thereafter kept at an elevated temperature.

Subsequently, the polymer solution is extruded through a spinning nozzle (for hollow fibres) or a slit nozzle (for flat film) into a fluid bath containing a nonsolvent for the polymer. The nonsolvent replaces the solvent and thus the polymer is precipitated to an inverted solid phase.

In the present invention the polymer solution preferably is extruded through an outer ring slit of a nozzle having two concentric openings. Simultaneously a centre fluid is extruded through an inner opening of the nozzle. At the outlet of the spinning nozzle the centre fluid comes in contact with the polymer solution and at this time the precipitation is initialised. The precipi-

The polymer solution preferably comprises 10-20 weight% of hydrophobic polymer and 2-11 weight% of hydrophilic polymer. The centre fluid comprises 45-60 weight% of precipitation medium, chosen from the group of water, glycerol and other alcohols, and 40-55 weight% of solvent.

In a preferred embodiment of the invention the polymer solution coming out through the outer slit openings is, on the outside of the precipitating fibre, exposed to a humid steam/air mixture. Preferably, the humid steam/air mixture has a temperature of at least 15°C, more preferably at least 30°C, and not more than 75°C, more preferably not more than 60°C.

Preferably, the humidity in the humid steam/air mixture is between 60 and 100% and the solvent content in the humid steam/air mixture is preferably between 0.5 and 5 weight%.

Before the extrusion suitable additives may be mixed into the mixture of the polymer solution. The additives are used to form a proper pore structure and optimise therewith the membrane permeability, the hydraulic and diffusive permeability and the sieving properties. The additives may be said to work as pore controller. In a preferred embodiment of the invention the polymer solution contains 0.5-7.5 weight% of a suitable additive, preferably chosen from the group comprising water, glycerol and other alcohols.

According to the invention the solvent may be chosen from the group comprising, n-methylpyrrolidon (NMP), dimethylacetamid (DMAC), dimethylsulphoxide (DMSO) dimethylformamide (DMF), butyrolactone and mixtures of said solvents.

According to a preferred embodiment of the invention of the invention, the conditions on the outside of the membrane and the combination with the polymer composition, centre fluid and temperature of the spinning nozzle, creates the optimal structure in a membrane according to the invention, i. e. four integral layers. Depending on the ratio of the components the four layers get different thickness.

It will be readily apparent to one skilled in the art that various substitutions and modifications may be

The present invention will now be illustrated by way of non-limiting examples of preferred embodiments in order to further facilitate the understanding of the invention.

Example 1

At the same time the 2 components (polymer & centre solution) enters a space separated from the room atmosphere. This space is called spinning shaft. A mixture of steam (100°C) and air (22°C) is injected into the spinning shaft. The temperature in the spinning shaft is adjusted by the ratio of steam and air at 52°C. The length of the spinning shaft is 890 mm. By the aid of gravity and a motor-driven roller, the hollow fibre is drawn from top to bottom, from spinneret through the spinning shaft into a water bath in vertical direction. The spinning velocity is 15.0 m/min. The hollow fibre is subsequently led through a cascade of water bathes and

temperatures increasing from 20 to 90°C. The wet hollow fibre membrane leaving the water rinsing bath is dried in a consecutive online drying step. After a texturising step, the hollow fibre is collected on a spinning wheel in the shape of a bundle. After introducing the bundle into a dialyser housing, it is potted with polyurethane, ends are cut, on both sides of the dialyser a header is fixed to the housing, the dialyser is rinsed with hot water and dried with air. During this last drying step, an amount of 19 g of residual water per m² effective membrane area is left on the dialyser. The filter device contains 1,1 m² effective membrane area. After labelling and packaging, the dialyser is steam-sterilized within the package in an autoclave at 121°C for 25 min.

Example 2 (Comparative)

Compared to example no. 1, only the following was changed in the composition of the polymer solution : 16 % of polyarylethersulfone, 0.5 % of Polyamide, 8 % of PVP K30, 0% of water and 75.5 % of NMP.

The composition of the centre solution was changed to: 48 % water and 52 % NMP .

The polymer solution temperature was 46°C, and the spinning shaft temperature was 42°C.

Example 3 (Comparative)

Compared to example no. 1, only the following was changed in the composition of the polymer solution: 14% of polyarylethersulfone, 0.5% of polyamide, 7% of PVP K30, 3% of water, and 75.5% of NMP.

The composition of the centre solution was changed to: 60% water and 40% NMP.

The polymer solution temperature was 53°C, and spinning shaft temperature was 48°C.

Results

The resulting properties of the hollow fibre membranes according to the examples are presented in the table below.

5

L_p = Hydraulic permeability of water (10^{-4} cm/s/bar).

C = Clearance Urea at $Q_B = 200$ ml/min, $Q_D = 500$ ml/min, $UF = 0$ (ml/min).

$S_{\beta 2M}$ = Sieving Coefficient for β -2-Microglobulin (MW=11,800) measured in whole blood.

S_{IL6} = Sieving Coefficient for Interleukin6 (MW=26,000) measured in whole blood.

S_{alb} = Sieving Coefficient for Albumin (MW= 68,000) measured in whole blood.

15

Example No.	L_p (10^{-4} cm/s/bar)	C (ml/min)	$S_{\beta 2M}$	S_{IL6}	S_{alb}	Pore size (nm)
1	218	181	0.98	0.95	0.011	20-40
2	190	182	0.99	0.98	0.146	>100
2	54	178	0.81	0.36	0.002	10-15

CLAIMS

1. A permselective asymmetric hollow fibre membrane for the separation of toxic mediators from blood,
 5 comprised of at least one hydrophobic polymer and at least one hydrophilic polymer,
 characterized in that said membrane allows passage of molecules having a molecular weight of up to 45 000 Daltons in presence of whole blood,
 10 and has a molecular weight exclusion limit in water of about 200,000 Daltons.
2. A membrane according to claim 1,
 characterized in that said at least one hydrophilic polymer and at least one hydrophobic polymer
 15 are present in the membrane as domains on the surface.
3. A membrane according to any of claims 1 or 2,
 characterized in that said at least one hydrophobic polymer is present in an amount of 50-80 weight%, based on the weight of the membrane.
- 20 4. A membrane according to any of claims 1-3,
 characterized in that said at least one hydrophilic polymer is present in an amount of 20-50 weight%, based on the weight of the membrane.
- 25 5. A membrane according to any of claims 1-4,
 characterized in that said at least one hydrophobic polymer is chosen from the group consisting of polyarylethersulfone (PAES), polypropylene (PP), polysulfone (PSU), polymethylmethacrylate (PMMA), polycarbonate (PC), polyacrylonitrile (PAN), polyamide (PA),
 30 or polytetrafluorethylene (PTFE).
6. A membrane according to any of claims 1-5,
 characterized in that said at least one hydrophilic polymer is chosen from the group consisting of polyvinylpyrrolidone (PVP), polyethyleneglycol (PEG),
 35 polyvinylalcohol (PVA), and copolymer of polypropyleneoxide and polyethyleneoxide (PPO-PEO).

7. A membrane according to any of claims 1-6, characterized in that said membrane has at least a 3-layer asymmetric structure.

5 8. A membrane according to any of claims 1-7, characterized in that a separation layer is present in the inner most layer of the hollow fibre.

9. A membrane according to claim 8, characterized in that the separation layer has a thickness of $< 0.5 \mu\text{m}$.

10 10. A membrane according to any of claims 8 or 9, characterized in that the separation layer contains pore channels.

11. A membrane according to any of claims 1-10, characterized in that the pore size in the separation layer is 15-60 nm, preferably 20-40 nm.

12. A membrane according to any of claims 1-11, characterized in that the sieving coefficient for IL-6 in presence of whole blood is 0.9-1.0.

20 13. A membrane according to any of claims 1-12, characterized in that the sieving coefficient for albumin in presence of whole blood is below 0.05.

25 14. A membrane according to any of claims 1-13, characterized in that the openings of the pores on the outer surface are in the range of $0.5-3 \mu\text{m}$ and the number of said pores are in the range of 10,000 to 150,000 pores/ mm^2 , preferably 20,000 to 100,000 pores/ mm^2 .

30 15. Process for the preparation of a membrane according to claims 1-14 by solvent phase inversion spinning, comprising the steps of

35 a) dissolving the at least one hydrophobic polymer and the at least one hydrophilic polymer in a solvent to form a polymer solution,

b) extruding the formed polymer solution through an outer ring slit of a nozzle with two concentric openings,

c) extruding a centre fluid through the inner opening of the nozzle, and

d) subsequently washing and preferably drying the membrane, wherein the polymer solution comprises 10-20 weight% hydrophobic polymer and 2-11 weight% hydrophilic polymer.

16. Process according to claim 15, wherein the centre fluid comprises 45-60 weight% of a precipitation medium chosen from the group of water, glycerol and other alcohols.

17. Process according to any of claims 15 or 16, wherein the centre fluid comprises 40-55 weight% of solvent.

18. Process according to any of claims 15-17, wherein the polymer solution emerges from the outer slit opening is, on the outside of the precipitating fibre, exposed to a humid steam/air mixture.

19. Process according to claim 18, wherein the temperature of the humid steam/air mixture is at least 15°C, preferably at least 30°C, and not more than 75°C, preferably not more than 60°C.

20. Process according to any of claims 18 or 19, wherein the humidity in the humid steam/air mixture is between 60 and 100%.

21. Process according to any of claims 18-20, wherein the solvent content in the humid steam/air mixture is between 0,5 and 5 weight%.

22. Process according to any of claims 15-21, wherein the polymer solution contains 0.5-7.5 weight% of suitable additives.

23. Process according to any of claims 15-22, wherein the solvent is chosen from the group comprising, n-methylpyrrolidon (NMP), dimethylacetamid (DMAC), dimethylsulphoxide (DMSO) dimethylformamide (DMF), butyrolactone and mixtures of said solvents.

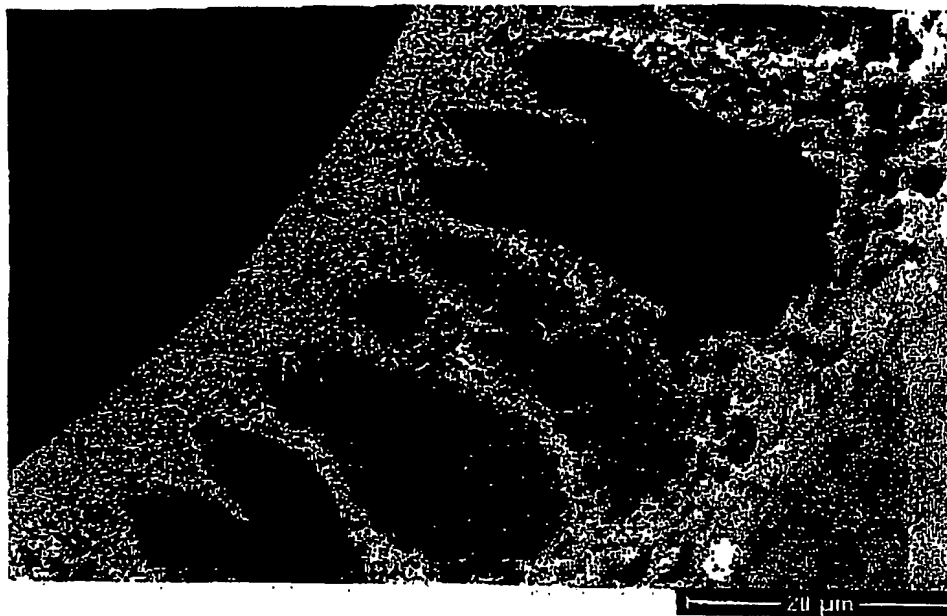
24. Process according to any of claims 15-23, wherein the temperature at the spinning nozzle and of the

20

ABSTRACT

The present invention relates to a permselective asymmetric hollow fibre membrane for the separation of toxic mediators from blood, comprised of at least one hydrophobic polymer and at least one hydrophilic polymer. Further, the present invention relates to a process for the preparation of such a membrane, and the use of said membrane in hemofiltration for treatment of toxic mediator related diseases.

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Fig 2

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Sieving Coefficients of Polyflux S (High Flux Membrane)
measured in whole blood and buffer (water) - solution

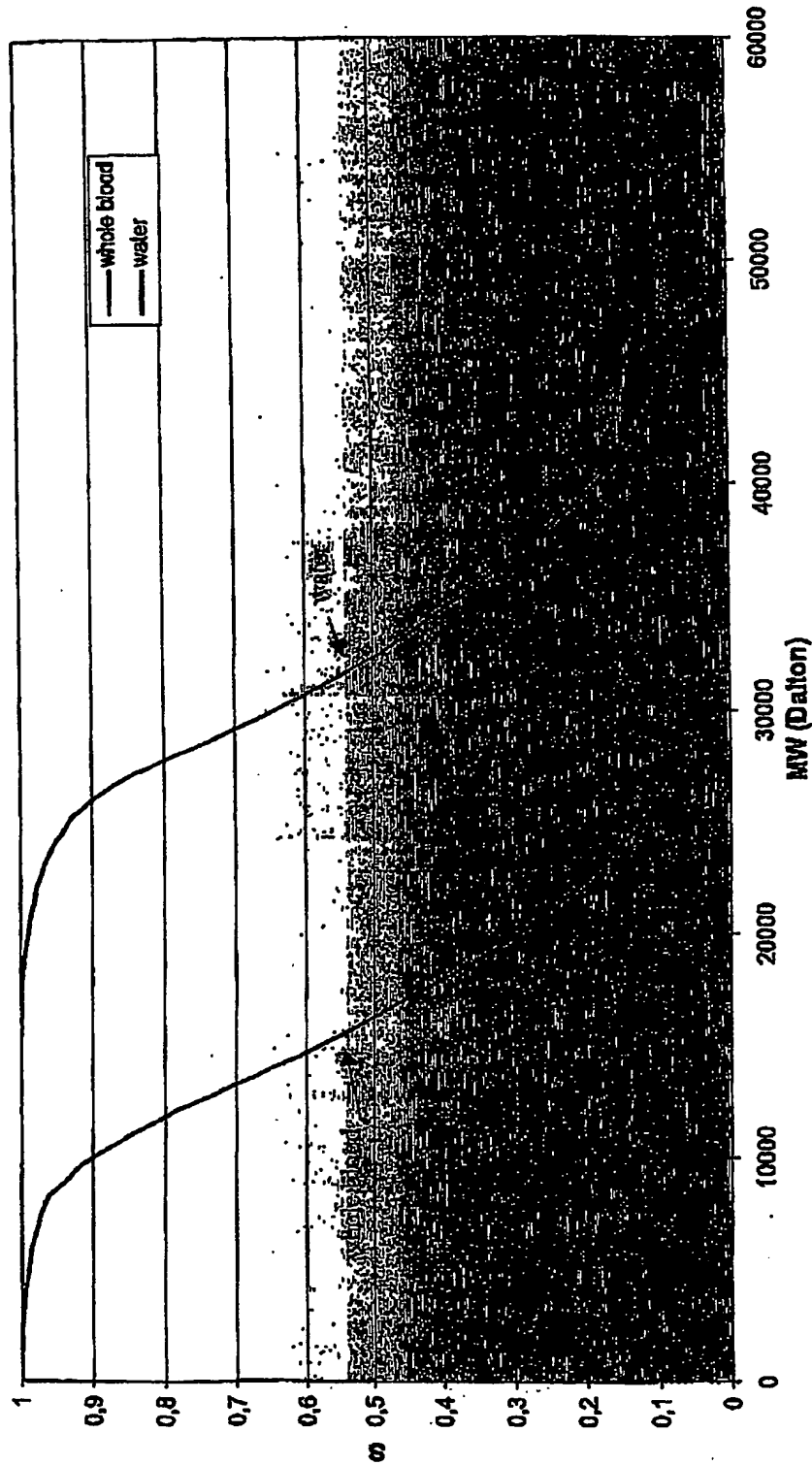


Fig 3a

Sieving Coefficients of High Cut Off Membrane
measured in whole blood and buffer (water) - solution

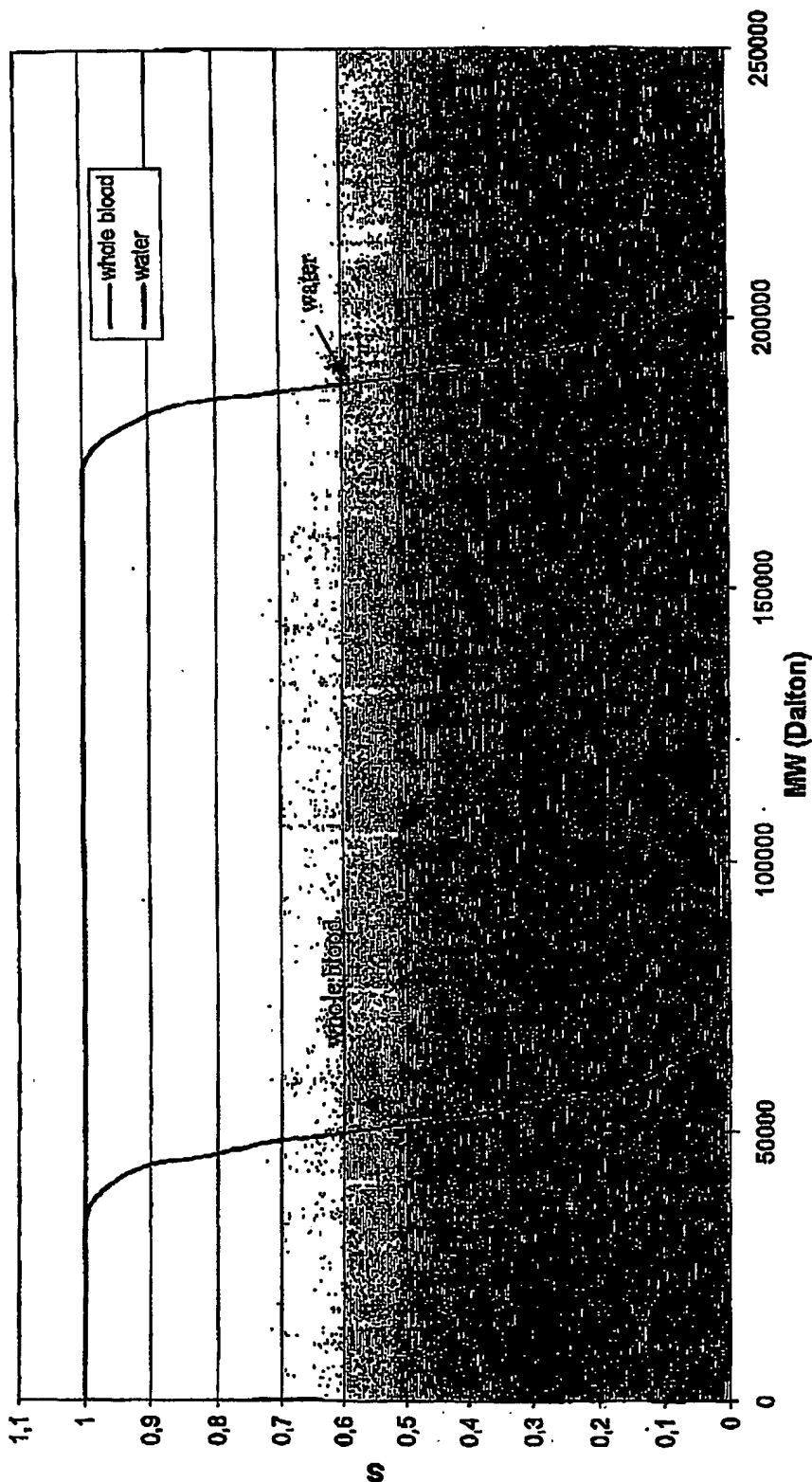


Fig. 3b

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Unit 1 Patient Laboratory

Date: 12/20

Patient Name: [illegible]

Protein loss into filtrate

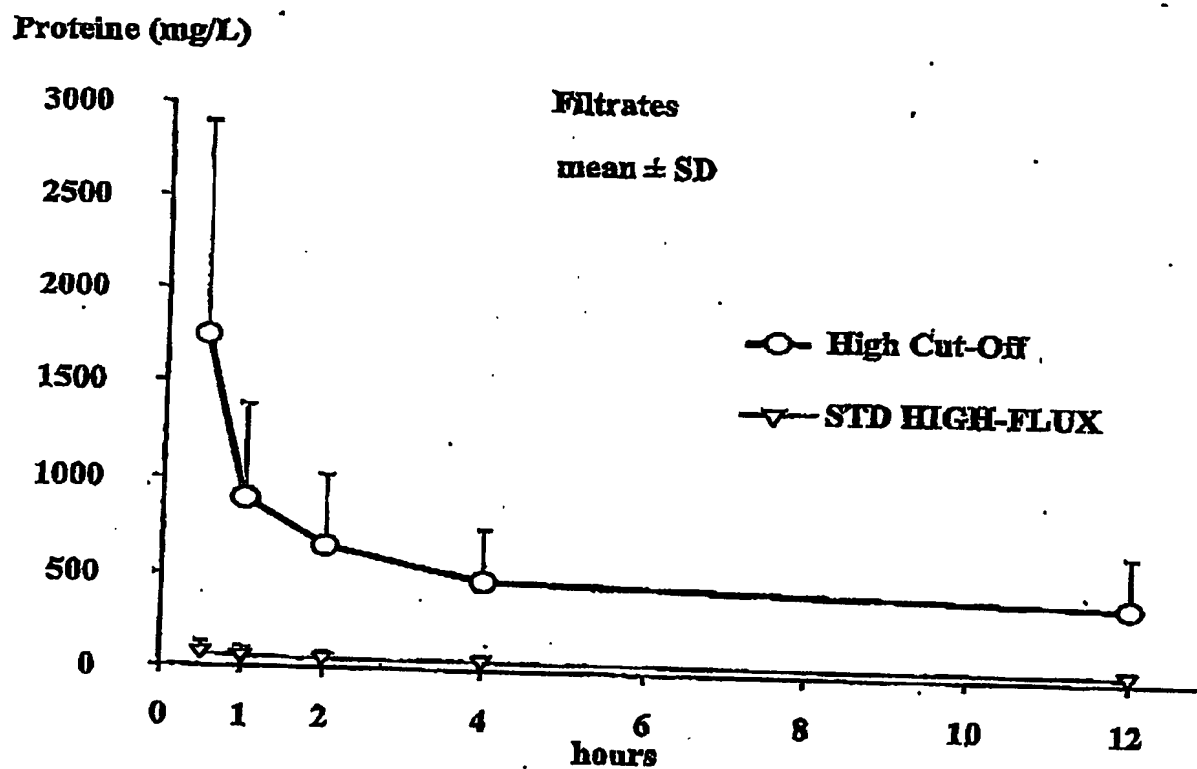


Fig 4

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Y-axis: Filtrate IL-6 [pg/ml]

X-axis: Plasma IL-6 [pg/ml]

Equation: $y = 0,99x$

R-squared: $R^2 = 0,99$

Condition: at $t = 0,5$ hr

	Interleukine-6 Sieving Coefficient				
	0,5 hr	1 hr	2 hr	4 hr	12 hr
High Cut-Off	0,92±0,31	0,93±0,32	0,93±0,30	0,88±0,28	0,75±0,33
30 kD std HF	0,03±0,05	0,01±0,03	0,01±0,02	0,01±0,02	0,00

Fig 5

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Hovind

Removal of circulating mediators I RIC/sepsis
-Acute renal failure

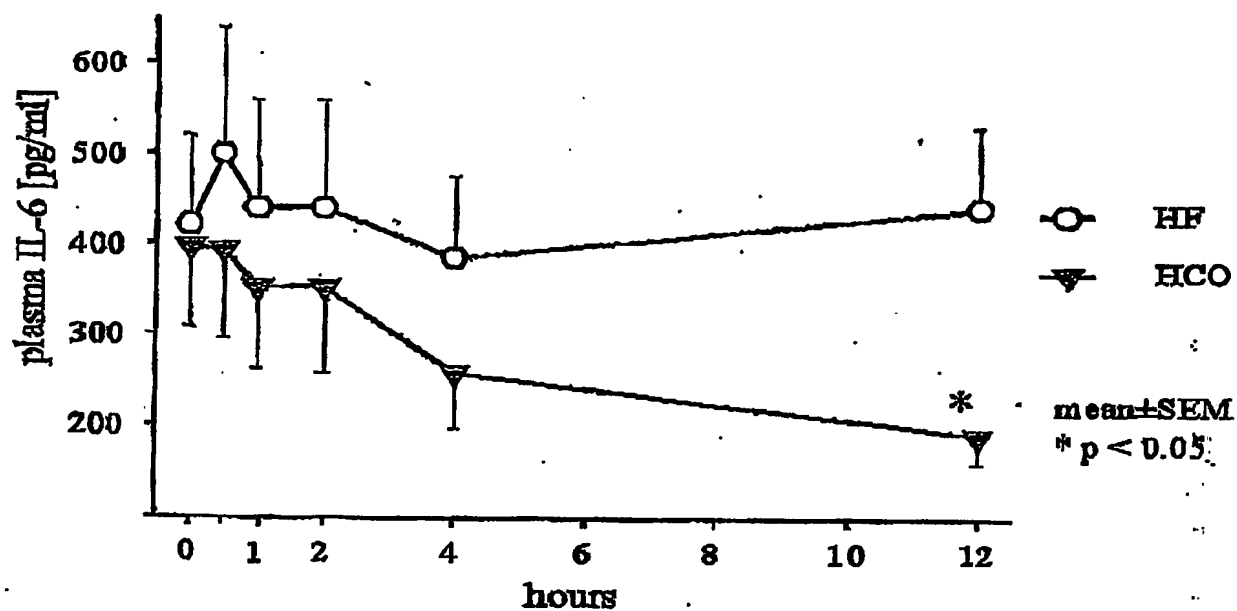


Fig 6

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